Research Program on Research Integrity Grant Abstracts - 2002

Trainee-Focused Training for Research Integrity
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The importance of the highest level of ethical and moral behavior among scientists is so universally accepted that it has become one of the "truths" which govern the scientific discovery process. Historically, young and developing scientists have learned what is expected of them when planning, doing and reporting research through the informal mechanisms inherent in the mentor-based training model research. As the complexities, opportunities, and size of biomedical research have expanded, however, concern has been raised that trainees are not acquiring the normative behaviors expected. This has led to the establishment expectations for systematic, formalized training in Responsible Conduct of Research (RCR). While this systematic training is well intended, prior studies have failed to identify meaningful impacts of such training, especially with respect to some of the most important behavioral expectations.

As present, it is unclear if failure to see impacts of RCR training is due to training design flaws, ineffective evaluation methodologies, intractability of research trainees, mixed messages they receive between courses and real life in the lab, or fundamental differences in the frames of references between current trainees and established scientists. The proposed research will take a step back from simply evaluating another RCR course to study in depth the frames of references for current trainees and the impacts of an RCR course from those frames of reference.

Using focus groups, individual interviews and qualitative research methods, the Aims will be to:

1. Work with faculty in the Mayo Graduate School course on RCR to define objectives and key messages for each topic
2. Establish the baseline perspectives on RCR for trainees at several levels of training
3. Determine trainee perceptions of the key messages provided in the RCR course
4. Specifically probe trainee perspectives before, immediately after, and one year after an RCR course on two key topics - Conflict of Interest and Authorship
5. Determine if trainees see consistency between messages provided in the course and their labs, and study the impact of inconsistencies on trainee attitudes and projected behavior
6. Identify high frequency perceptions or frames of reference which are substantially at odds with accepted research norms and begin designing better interventions to alter them

New Graduate Students' Baseline Knowledge of RCR

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Educational institutions play a vital role in preparing students to practice ethically throughout their professional careers. It is increasingly evident, however, that students enter biomedical science graduate programs with experience in and perspectives on scientific practice that shape their acceptance of instruction on the responsible conduct of research (RCR). Thus insight into what entering graduate students know about the concepts and standards of RCR is crucial to the successful design and implementation of training programs in research integrity.

The long-range goal of this research is to stimulate and reinforce ethical behavior among biomedical science students during their graduate education and subsequent careers through well-designed and well-implemented RCR courses. The objectives of this study are to evaluate the baseline knowledge and understanding of RCR among incoming graduate students at four academic health science centers and to identify how these students gained the knowledge. The hypothesis to be tested is that new graduate students have widely variable knowledge of the ethical standards of scientific research and widely variable levels of experience in their application. This hypothesis will be tested through: 1) the development of an objective test on the core concepts and standards of RCR that can distinguish among a variety of levels of education and experience; 2) the administration of this test to a cohort of entering graduate students in four academic health science centers; 3) a survey of this same cohort to identify the sources of their knowledge and understanding of the core concepts and standards of RCR and perceptions of their value; and 4) assessment of the variability in knowledge and understanding this cohort's members in relation to gender and the country in which they received their undergraduate science education.

The results of this research will help faculty and program directors charged with RCR education focus their teaching objectives and refine their methods by identifying areas in which students are most likely to misunderstand or be ignorant of essential concepts in scientific integrity. The test itself will also be readily adaptable to the evaluation of specific groups of students and others preparing for RCR instruction.

Effectiveness of RCR Instruction

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Despite an eleven year history of mandated instruction in responsible conduct of research (RCR), little is known about the effectiveness of such training. The evaluation of RCR instruction has largely been limited to individual courses. Typically, instructors set course goals and objectives and use teaching tools to evaluate mastery of skills. There has been no systematic effort to determine if RCR instruction has measurable effects on awareness, attention, and behavioral judgments related to research ethics. To shed light on RCR instruction effectiveness, we shall conduct a national longitudinal study of biomedical, behavioral, and clinical research postdoctoral trainees supported by NIH F32 Fellowships. We shall use a 3-wave survey to measure awareness, attention to, and behavioral judgment pre- and post-RCR instruction in one core area of RCR content, authorship and publication practices. Our a 3-wave panel design will allow the measurement of the key dependent variables (awareness, attention, and behavioral decisions) prior to RCR instruction, shortly after RCR instruction, and then after a longer time has elapsed post-RCR instruction. We shall disseminate our findings and interpretations in the peer-reviewed literature and on the internet. We believe that the results of our broad-based, systematic approach will provide a foundation for understanding RCR teaching effectiveness and for suggesting strategies to improve it. Although our study focuses solely on a authorship and publication practices, we expect our approach will set the stage for parallel studies in other core topic areas.

A Qualitative Study of Editorial Decision-Making

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The overall goal of this study is to identify and explain systematic biases in the editorial decision-making process by examining the factors that influence editors' decisions to accept or reject articles for publication in biomedical journals. We will study editorial practices, processes, and outcomes at four major biomedical journals in the US and the UK: *Journal of the American Medical Association, Annals of Internal Medicine, The Lancet,* and the *British Medical Journal.* We will identify the factors that influence editors' decisions to publish manuscripts, and identify sources of systematic bias in the editorial review process that may results in a publication record that is not representative of the true distribution of study findings submitted to each journal. Using multiple qualitative methods, including interviews, ethnographic observation, and conversation analysis, we will address the following Specific Aims:

1. Describe the characteristics of the editors, reviewers, authors, and articles submitted for publication;
2. Describe the editorial process whereby articles are considered, reviewed, and accepted or rejected;
3. Identify the explicit and implicit criteria used by editors and reviewers in evaluating manuscripts;
4. Describe the social interactional features of the editorial meetings as editors reach collective decisions regarding particular manuscripts;
5. Evaluate the effectiveness of the editorial decision-making process in ensuring that the true distribution of study findings submitted is represented and that important scientific results are published fairly and quickly.

We hypothesize that *manuscript characteristics* (such as study design, originality, topic, and direction and statistical significance of the findings), *author characteristics* (such as institutional affiliation, funding source, and conflict of interest statement), *organizational characteristics* (such as number of competing papers and number of slots available in the issue to the journal, the distribution of topics in the issue), as well as the *social interactional features of the editorial meeting itself* (such as the initial characterization of the paper by the lead editor, strength of positive or negative assessments, and degree of conflict or disagreement) will combine to produce decisions that ultimately favor studies with statistically significant findings over those with statistically nonsignificant findings.

Nurses: Research Integrity in Clinical Trials

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Research integrity is, appropriately, a national priority. However in discussions of clinical trials, research ethics focuses nearly exclusively on the perspective of principal investigators. Yet nurses are key in implementing clinical trials, that is, they perform much of the day-to-day work. While the ethical issues pertaining to physician-researchers are well documented, there is virtually no research on the ethical concerns and challenges confronting nurses working in clinical trials. There is some evidence indicating that their perspective differs from that of physician-researchers at least in certain circumstances. Also, the complexity of clinical trials suggests that the ethical concerns encountered by nurses might vary by disease being studied, type of trial, site of trial, source of funding, and other variables. In order to move towards a more complete knowledge of the ethical issues arising in research, it is crucial that we know more about the ethical concerns and challenges of nurses who implement clinical trials and the institutional and other factors influencing these concerns and challenges. Assurance of research integrity requires that policies and guidelines be based on such an adequate understanding of the concerns and challenges faced in the work of clinical trials. The specific aims of this research are to: 1) identify and describe the ethical and professional concerns encountered by nurses during their work in clinical trials; 2) identify and compare the institutional and other conditions that influence the nurses' ethical/professional concerns; 3) describe the process nurses use in making ethical decisions within clinical trials; 4) identify sources of guidance/resolution for difficulties that clinical trials nurses have used to promote research integrity. Eight focus groups of nurses working in four disease-related clinical trials will be conducted in two regions of the country. The four diseases are addictions/mental health, breast cancer, Parkinson's Disease, and cardiovascular disease. This study hypothesizes that clinical trials investigating these four diseases will be associated with different ethical challenges and institutional factors. The sample will consist of 8 to 10 nurses per focus group with two focus groups for each disease. Demographic data including education level, specific training in ethics, and previous experience in clinical trials work will be collected. Consensual qualitative analysis will be the primary method used for analyzing focus group data. This data will serve as a basis for future research, with two long-term goals for the research program. The first will be to evaluate the adequacy of existing policy and guidance for the research involving human participants, which has been developed without an understanding of the concerns confronting nurses in their work in clinical trials. The second will be to reconsider the dominant understanding of the ethics of research, which conceives of moral decision-making as the application of abstract, impartial moral rules and tends to ignore the moral importance of context, such as the institutional and other factors we propose to investigate.

Industry-Sponsored Research Contracts: An Empirical Study

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The aim of the study is to examine policies, practices, and institutional norms concerning the allocation of control over various aspects of industry-funded clinical trials between academic investigators and sponsors. Industry funding has become an indispensable part of biomedical research, accounting for 70% of the funding for clinical drug trials in the U.S. While academic-industry research partnerships carry great benefits, the terms of the contracts between academic institutions and sponsors pose a possible threat to research integrity in that they may restrict investigators' academic freedom. There exists scant empirical data on the nature and consequences of these legal relationships. This study explores five research questions: (1) What institutional structures (such as formal policies and consultation with legal counsel) are in place in academic medical centers to negotiate contracts for industry-sponsored clinical trials? (2) How frequently do contracts between academic institutions and industry sponsors contain provisions relating to control over data, control over the conduct of the trial, control over publication, and confidentiality? (3) To what extent do contract officers and faculty view it as acceptable or unacceptable to cede control over each of these aspects of clinical trials to industry sponsors? (4) What is the incidence and nature of disputes with industry sponsors? (5) Do the answers to Questions 1 through 4 vary according to institutional and faculty characteristics (institutional size, faculty academic rank, faculty specialty, and percentage of funding from industry)? We hypothesize that respondents will report that allocation of control over many aspects of clinical trials to industry sponsors is acceptable, but that large institutions, institutions with formal policies governing industry-sponsored research, faculty with senior academic rank, and faculty with little industry funding will be less likely than other institutions and faculty to view sponsor controls as acceptable. We further hypothesize that the use of formal policies will be associated with a lower incidence of investigator-sponsor disputes. These hypotheses will be tested through a mailed survey of grants and contracts administrators and clinical faculty at academic medical centers. The survey will gather information on institutional policies and procedures, the acceptability of specific types of sponsor controls, disputes with sponsors, and perceived pressures in the research environment. The data will be analyzed descriptively and with chi-squared tests and regression analysis.

Motivating Integrity in Research with Human Subjects

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NIH and other institutional bodies have mandated training to increase researchers' knowledge of research ethics and awareness of the standards that regulate research integrity. Educational initiatives aim to uphold the integrity of the profession of scientific inquiry and, when research involves human subjects, ensure adequate protection of their safety. Our project will provide a basis for assessing and improving educational efforts, by evaluating factors that may hinder responsible conduct in research involving human subjects. We hypothesize that researchers may be influenced by professional climate, institutional social structures, and ethical norms that derive
from sources other than research integrity guidelines. One of our project aims is to define these challenges, which may present barriers to responsible conduct of research with human subjects. Efforts to ensure compliance with standards for research integrity are likely to succeed only if they explicitly acknowledge and address barriers to compliance. This project will assess the presence and importance of such barriers through information gathered in interviews and focus groups with researchers and other key informants. Data will be assessed using frameworks derived from the social sciences. Additionally, the information gathered will inform the development of institutional and researcher self-assessment tools to be used to promote more collegial and productive research environments through local educational efforts.

Correcting The Literature After Scientific Misconduct

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The purpose of this study is to investigate the nature and scope of the corrections made to the published biomedical literature affected by scientific misconduct and to make recommendations to the appropriate entities when warranted by the results of the study. This retrospective cohort study will involve the following steps. 1) Identify all Office of Research Integrity (ORI) determinations of scientific misconduct from 1992-2001, and select for inclusion in the study cohort those individuals with ORI-identified publications containing plagiarism, misrepresentation of data or other information requiring correction, errata, retraction, or similar actions (problem publications). 2) Conduct searches in MEDLINE-based bibliographic and citation databases to determine the extent to which errata, corrections and retractions (corrigenda) are tagged to the bibliographic citations of such problem publications, and characterize the range of the location and content of such postings. 3) Describe how the publishers and vendors of electronic databases identify errata, retractions and other forms of notification within their online citations. 4) Describe the extent to which subsequent authors cite the problem publications. Determine if those who cite the problem publications also cite the ORI finding of misconduct, or the corrigenda (for those problem publications that are tagged with such corrigenda). 5) Randomly sample the citations to the problem articles and conduct a content analysis to determine the nature of the reference to the problem publication. Preliminary studies have demonstrated the nature and extent of the problem of correcting the literature after scientific misconduct. Preliminary work has also demonstrated the feasibility of the proposed methodology. Based on the study findings, we will formulate policy recommendations to appropriate entities for improving the integrity of the published biomedical literature. We will also disseminate the study findings by developing an awareness program related to maintaining the integrity of the published literature for professional library associations and societies, and through peer-reviewed publications.

Equipoise and the Research Integrity of Clinical Trials

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We recently demonstrated that the major threat to research integrity in clinical trials may be due to a violation of the equipoise or "the uncertainty principle", the fundamental principle on which nearly the entire system of human experimentation stands. This principle states that the patient should be enrolled in a randomized controlled trial (RCT) only if there is substantial uncertainty about which of the trial treatments would benefit a patient most. We hypothesize that there is a relationship between equipoise and trials outcomes. If the investigators do not *know* in advance what they are going to discover, and if the uncertainty principle is observed and the literature on experimental therapies is fairly complete, we would expect, over time to find no significant difference between the proportion of published results that favor experimental treatments and those that favor comparison treatments. We have performed an earlier investigation on this issue and found that this expected distribution of outcomes was observed among those published trials that were funded by public resources, but that the uncertainty principle appeared to be violated among those published trials funded by pharmaceutical companies. However, we could not exclude publication bias as the explanation for the higher proportion of positive results in the literature. Based on other studies, failure to publish could be as high as 51%. Furthermore, we could not contrast our data with expected distributions of outcomes in clinical trials, since this has not been determined. Therefore, the real relationship between the uncertainty principle and outcomes of RCTs remains unsettled.

To elucidate this relationship, we proposed to study a comprehensive population of initiated RCTs from a unique funder (using an inventory of the NCI-sponsored trials). Our hypothesis will be addressed through the following **specific aims**:

1. All National Cancer Institute (NCI)-sponsored RCTs trials funded in the years 1975 through 2001 will be identified using the NCI registry of clinical trials in cancer
2. We will identify the primary and additional outcomes selected for study by the investigators.
3. We will review the trials (published and unpublished) to classify their primary and other outcomes, specifically whether the innovative or comparison treatment was preferred.
4. We will perform analyses for evidence of investigators' equipoise, and for the relationship of outcome to study quality, type of comparison treatment, investigator characteristics, and funding source

Since violation of the principle of equipoise and publication bias represent two of the most serious threats to the integrity of the research process in RCTs, it is of long-term significance to understand the extent to which these factors are evident in the study of RCTs. By understanding these relationships, we will be in a position to contribute to the preservation of a system of high quality clinical trials in medicine. This proposal will answer both the question "what do trials do for us?" and assess the reliability of the research in which public has invested so much.